REMARKS

Amendment summary

Claim 1 is amended to recite that the biologically active compound is associated hydrophobically with the copolymer in the core of the micelles. Support for this amendment may be found, e.g., in the paragraph bridging pages 2-3 of the present specification. In addition, subject matter from Claims 14, 43, and 44 has been incorporated into Claim 1. Additional support for the amendment may be found, e.g., in the paragraph at the top of page 13 of the present specification.

The subject matter from Claims 59 and 60 has been incorporated into Claims 57 and 58, respectively.

Claim 61 is added. Support for this claim may be found, e.g., at page 8, lines 17-20, the paragraph at the top of page 13, and Example 1 of the present specification.

Claims 13-16, 21-23, 43-44, and 59-60 have been canceled.

No new matter is added by this Amendment, and Applicants respectfully submit that entry of this Amendment is proper.

Status of the claims

Claims 1, 7-16, 21-28, 38, 43, 44, and 57-60 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Lobb et al. (J. Am. Chem. Soc., 2001) in view of Kataoka et al. (Adv. Drug Delivery Rev., 2001), evidenced by Dalmark et al. (J. Gen. Physiol., 1981) (hereinafter "Lobb," "Kataoka," and "Dalmark," respectively). Claims 20 and 42 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Lobb in view of Kataoka and Coessens et al. (Prog. Poly. Sci., 2001) (hereinafter "Coessens"), evidenced by Dalmark.

Response to claim rejections

With respect to independent claims 1 and 61, Applicants respectfully traverse the rejections on the basis that (1) Applicants have shown the unexpected results that flow from the use of the presently recited diisopropylamino ethyl group. With respect to independent Claims 57 and 58, Applicants additionally traverse on the basis that a person having ordinary skill in the art would not consider the disclosure of Kataoka with respect to the polymer types of Lobb when determining a suitable block copolymer for use with cytotoxic actives.

Applicants first note that the basis for the rejections set forth in the Office Action is that "Lobb fails to specifically teach the [presently claimed] species of diisopropylamino ethyl phosphate inner salt," but "one would have been motivated to substitute diisopropylamino ethyl methacrylate for (diethylamino) ethyl methacrylate because the two monomers differ by the presence of a methyl group. The presence of a methyl group in place of a hydrogen does not give patentable momentum to the recited species." See Paragraph Nos. 20 and 22 of the Office Action. According to this passage of the Office Action, "it is well established that a methyl is structurally analogous to a hydrogen, and absent any secondary result, the elected species would possess the same functional properties as that of diethyl ammonium."

Applicants respectfully submit that the Examiner has overlooked the unexpected results which are shown in the present specification, where the diethylamino ethyl group of the monomer in Lobb (diethylaminoethyl methacrylate (DEA)) is replaced by the diisopropylamino ethyl group in the polymer which is a component of the composition of present claims 1 and 61.

Applicants have shown two unexpected results of the presently claimed invention. First, the MPC-DPA corresponding to the presently claimed invention forms micelles at physiological

pH's, which is important for its use in human and animal applications, whereas MPC-DEA does not form micelles at physiological pH's. Second, MPC-DPA polymers have been shown in the present specification to have properties that are not temperature dependent, whereas MPC-DEA polymers' properties have been shown to be temperature dependent. Applicants have shown these results by replacing DEA with DPA in the experiments shown in the present specification.

With respect to the formation of micelles at physiological pH's, Example 7 of the present specification shows a comparison of the pH at which block copolymers of MPC with either DEA (e.g., as in Lobb) or DPA (as presently claimed) form micelles. As indicated in Example 7, page 31, lines 12-14 of the present specification, the MPC-DEA block copolymers do not form micelles at pH 7.4 - they only form micelles at higher pH values. Micelle formation for MPC-DEA block copolymers takes place at pH 8, as shown in Example 5. See page 30, lines 10-14 and Figure 6 of the present specification. By contrast, as indicated in Example 7 of the present specification, block copolymers of MPC and DPA form micelles at pH 7.4, the micelles being useful for loading hydrophobic drugs. This difference between MPC-DEA and MPC-DPA is further illustrated in Table 4 of the present specification, which shows that the MPC-DEA block copolymers are in unimer form at pH 7.4 (at 25°C), the particle sizes measured by PCS being less than 20 nm. By contrast, however, at pH 7.4 the MPC-DPA block copolymers form micelles, that is they have a larger particle size, in this case 30-50 nm.

Example 13 further illustrates these unexpected results. In Example 13 of the present specification, tests were carried out comparing the performance of MPC-DEA and MPC-DPA block copolymers using the hydrophobic dye pyrene as model drug. As explained, pyrene fluorescence is a sensitive technique for detecting the formation of block copolymer micelles. Pyrene is highly hydrophobic and has a low solubility in water such that it migrates preferentially into the hydrophobic micelle cores. A red shift is observed in the pyrene

fluorescence spectrum and there are also changes in relative peak intensities for the vibrational fine structure (I_1/I_3 ratio). Figure 20 shows the variation in the intensity ratio I_1/I_3 against solution pH for the block copolymers. Figure 20 shows that the intensity ratio shifts at a lower pH for the DPA block copolymer than for the DEA block copolymer. The difference between the pH values at which this shift occurs, that is at which micellisation occurs, is consistent with the results of Example 7 discussed above.

Applicants note that the consequence of the difference between the pH values at which micellisation occurs is extremely important for compositions useful for administration to a human or animal. Since the block copolymers of MPC-DEA are not in micellar form at pH 7.4, a hydrophobic drug cannot be provided in the form of a micellar composition in such copolymers at that pH. The higher pH's at which these copolymers do form micellar compositions are, however, less suitable for human or animal administration, since they are not physiological pH's. By contrast, compositions of MPC-DEA block copolymers are in micellar form at a physiological pH (i.e., pH 7.4), so that compositions suitable for administration to humans and animals may be provided comprising micelles containing hydrophobic drug dispersed in the core.

This difference in micellisation properties between MPC-DEA and MPC-DPA block copolymers is a very important difference for forming compositions having potential therapeutic utility for administration to human or animal subjects. Nothing in Lobb would lead a person having ordinary skill in the art to expect that the substitution of the MPC-DEA block copolymer by MPC-DPA block copolymer would have this effect.

With respect to the temperature dependent properties of MPC-DEA versus the temperature independent properties of MPC-DPA, Example 7 and a comparison of Tables 3-5 is illustrative. As is explained on page 34 of the present specification, the MPC-DEA block

copolymers have a temperature dependent performance. That is, the behavior of the block copolymers at different pH's are heavily dependent on the temperature. This is seen by the behavior of the block copolymer at pH 8, where the behavior is different at 5°C compared to 25°C and is different again compared to 70°C. By contrast, it is illustrated that the two block copolymers of MPC-DPA have no temperature dependency - they behave in the same manner at 4°C, 25°C and 75°C. At low pH, for instance pH 4, the MPC-DPA block copolymer is in unimer form (the particle size is less than 20 nm), whereas at pH 7.4, regardless of temperature, micelles are formed (that is, the particles have larger sizes). This temperature sensitivity for MPC-DEA block copolymers could be a significant problem during the production and storage procedures for compositions based on that copolymer. Accordingly, the temperature stability for MPC-DPA block copolymers is likely to be very advantageous. Again, a person having ordinary skill in the art reviewing Lobb would not expect the reported difference between the behavior of DPC-DEA and DPC-DPA block copolymers in terms of temperature dependence.

Accordingly, Applicants respectfully submit that the present specification illustrates the unexpected results that are obtained in the substitution of the diethylamino ethyl group in Lobb by diisopropylethyl amino specified in claim 1.

With respect to Claim 57, Applicants respectfully submit that the position set forth in the Office Action, that "OEGBr is a hydrophobic polymer" is incorrect. See page 12, line 4 of Office Action. Oligo(ethylene glycol) is a hydrophilic block. Accordingly, a block copolymer of oligoethylene glycol-MPC would not be a block copolymer having a hydrophilic block and a hydrophobic block as required by claim 57, but would instead be a block copolymer having two hydrophilic blocks. As such, the copolymer would not form micelles. Applicants note that in Example 2, block copolymers are formed using oligoethylene glycol as initiator, a polypropylene glycol analogue, and PDMS based macro initiators. The product of the PEO-based

polymerisation does not form micelles. Applicants acknowledge that this is not stated explicitly in the Example, but is the reason why the block copolymer was not subjected to performance tests in Example 3. In Example 3 it is shown that the PPO-MPC block copolymer does form micelles, this being a temperature-dependent process. In view of the above, Lobb does not anticipate or render obvious the subject matter of Claim 57 because it does not disclose or suggest a block copolymer formed from a hydrophobic polymer-based initiator. Applicants note that Kataoka does not remedy this deficiency in Lobb.

Further, with respect to Claim 58, which recites the presence of a cytotoxic biological compound, Applicants respectfully submit that a person having ordinary skill in the art reviewing Kataoka would not have a reason to believe that the block copolymers in Lobb would be useful in delivering doxorubicin. First, nowhere does Kataoka disclose block copolymers in which the hydrophilic and hydrophobic block are each formed by the polymerisation of ethylenically unsaturated monomer, as recited in present Claim 58. Rather, the block copolymers described in Kataoka are of a very different type, none having hydrophilic blocks formed of ethylenically unsaturated monomers. In fact, the only reference in Kataoka to polymerisations involving ethylenically unsaturated monomers is in Section 8, which concerns DNA actives - not hydrophobic actives and not cytotoxic actives. The block copolymers used to deliver doxorubicin in Kataoka, for instance described in Section 2, are very different types of block copolymers, wholly dissimilar to those described by Lobb, and distinct from those to which present Claim 58 is directed. Accordingly, a person having ordinary skill in the art would not consider the disclosure of Kataoka in respect of the polymer types of Lobb when determining a suitable block copolymer for use with cytotoxic actives. For at least this reason, Claim 58 is not obvious over Lobb in view of Kataoka.

In view of the above, Applicants respectfully submit that the presently claimed invention is not anticipated by or rendered obvious by the cited references. Accordingly, Applicants respectfully request the reconsideration and withdrawal of these rejections.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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